

Droxidopa (NORTHERA™)**National Drug Monograph****December 2014****VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹**Description/Mechanism of Action**

Droxidopa is a synthetic amino acid analog that is metabolized by dopa-decarboxylase to norepinephrine. Norepinephrine increases blood pressure through peripheral arterial and venous vasoconstriction.

Indication(s) Under Review in this document

Droxidopa is indicated for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of droxidopa should be assessed periodically.¹

Dosage Form(s) Under Review

Droxidopa is available as 100 mg, 200 mg, 300 mg hard gelatin capsules.

REMS

☐ REMS ☒ No REMS

See Other Considerations for additional REMS information

Pregnancy Rating

Droxidopa is Pregnancy Category C.

Executive Summary**Efficacy¹⁻³**

- Patients with symptomatic NOH treated with droxidopa experienced an improvement in symptoms compared to placebo as measured by the change in the Orthostatic Hypotension Questionnaire (OHQ) overall composite score (primary endpoint: droxidopa -1.83 vs. placebo -0.93; difference 0.90, P=0.003), composite symptom score and composite symptom-impact score (secondary endpoints)
- Treatment with droxidopa increased standing systolic blood pressure compared to placebo (difference 7.3 mm Hg; P<0.001)

Safety¹⁻³

- Boxed Warning for Supine Hypertension: Monitor supine blood pressure prior to and during treatment with droxidopa and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue droxidopa.
- Case reports of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with droxidopa during post-marketing surveillance. Patients should be observed carefully if the dose of droxidopa is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. Although NMS is uncommon, it can be life-threatening where early diagnosis is important to ensure appropriate treatment. NMS is characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes.
- Data with use of droxidopa open-label is available for ≥ 2 years; however, there is limited data for long-term use at the highest dose and no long-term controlled trials

Other Considerations¹⁻⁴

- Only patients who responded to droxidopa during the initial titration period were enrolled in the pivotal trial Study 301
- Benefit with droxidopa not seen past 2 weeks in clinical trials

December 2014

Updated version may be found at www.pbm.va.gov or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx>

Potential Impact ^{1,3-13}	<ul style="list-style-type: none"> • No direct comparison trials with other drug therapies used for NOH • Projected place in therapy: Although limited data (and not FDA approved for orthostatic hypotension or NOH), fludrocortisone has been used for orthostatic hypotension, if symptoms are not managed by non-pharmacologic measures. Besides droxidopa, midodrine is the only other FDA approved treatment specifically for NOH. Other treatments have also been used for orthostatic hypotension, most with limited data. Results of comparison trials with droxidopa are not available at this time; place in therapy should be determined based on patient response, tolerability, convenience, and cost of treatment. Initial patient response to droxidopa should be assessed, with continued effectiveness of droxidopa reassessed periodically.
------------------------------------	--

Background

Purpose for review

Recent FDA approval.

Issues to be determined:

- ✓ Does the evidence show that droxidopa is effective for the treatment of NOH that translates into a clinically meaningful benefit, including a decrease in the incidence and severity of symptoms, and improvement in functional capacity?
- ✓ Does droxidopa improve fall risk?
- ✓ Does droxidopa offer advantages to currently available alternatives?
- ✓ Does droxidopa offer advantages over current VANF agents?
- ✓ What safety issues need to be considered with the use of droxidopa?
- ✓ Does droxidopa have specific characteristics best managed by the non-formulary process or criteria for use?

Other therapeutic options^{2,4-10,12,13}

Midodrine is also available with an FDA indication for symptomatic NOH. Midodrine was approved based on an increase in standing systolic blood pressure (SBP), considered a surrogate endpoint reasonably likely to predict clinical benefit.² Additional studies also report symptomatic improvement with midodrine in patients with NOH.^{4-8,13} Fludrocortisone has also been used in patients with NOH, with limited data, but is not FDA approved for this indication.^{2,4,9-10,12} Additional pharmacologic agents have been used off-label for NOH: desmopressin, dihydroergotamine, indomethacin, pyridostigmine, erythropoietin,^{2,4} as well as other agents; most of which have limited data.^{4,10}

Select Formulary Alternatives	Other Considerations
Midodrine	<p>FDA approved for symptomatic NOH</p> <p>Efficacy: Midodrine statistically significantly improved standing SBP vs. placebo (3 weeks, N=171) in patients with NOH. Symptoms of lightheadedness improved with midodrine vs. placebo throughout trial (2 weeks, P=0.02; 3 weeks, P=0.06). Global symptom relief score statistically significantly improved with midodrine vs. placebo.^{6,13} Midodrine (10mg dose) increased standing SBP vs. placebo (P<0.001); and improved symptoms of dizziness, weakness/fatigue, syncope, energy level, standing > 15 minutes, depression (P<0.05 depending on the dose) in a 4 week trial of 97 patients with NOH.^{7,13}</p> <p>Dosing: 2.5 to 10 mg three times daily (usual dose 5 to 10 mg three times daily; e.g., before arising, before lunch, mid-afternoon,⁸ avoid giving within 4 hours of bedtime)</p> <p>Adverse Events: supine hypertension; paresthesia; dysuria; piloerection; pruritus</p> <p>Use with caution in renal or hepatic impairment</p>
Fludrocortisone	<p>Off-label for symptomatic NOH</p> <p>Efficacy: Limited controlled trial data;^{9,10,12}</p> <p>Supine and tilted SBP statistically significantly increased with</p>

fludrocortisone compared to placebo (3 weeks, N=6) in patients with diabetic autonomic neuropathy.^{9,12} Statistically significant improvement in orthostatic symptoms with fludrocortisone plus nonpharmacologic treatment compared to nonpharmacologic treatment alone (3 week trial, N=17) in patients with Parkinson's disease.¹² Fludrocortisone allowed as adjunct therapy in trials evaluating efficacy of other therapies (e.g., midodrine 46% of patients,⁶ droxidopa 29%¹). Dosing: 0.1 to 0.4 mg daily (once or divided twice daily)^{4,9,12}. Adverse Events: supine hypertension; hypokalemia; fluid retention. Use with caution in patients with renal insufficiency.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1976 to October 2014) using the search terms droxidopa, L-DOPS, L-threo-3,4-dihydroxyphenylserine. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. Randomized controlled Phase 3 trials published in peer-reviewed journals evaluating the FDA approved indications were included. Medical reviews on the FDA Web site were also reviewed for additional information.

Review of Efficacy

- FDA approval of droxidopa was based on one trial (Study 301) of four that were submitted during the initial application, as well as data from an additional trial (Study 306B) submitted for subsequent review.
- Results from Study 301 demonstrated a statistically significant improvement in symptoms of NOH at Week 1, as measured by a change in the Orthostatic Hypotension Questionnaire (OHQ) overall composite score (primary endpoint), as well as the OHQ composite symptom score and composite symptom-impact score (refer to details below). Patients receiving treatment with droxidopa also experienced a greater increase in standing systolic blood pressure compared to placebo.
- The beneficial effect of droxidopa for symptomatic NOH past 2 weeks of treatment has not been demonstrated.
- Whether treatment with droxidopa prevents falls, or improves activities of daily living or quality of life, in patients with symptomatic NOH has not been established.
- Results from direct comparison trials are not available to determine how droxidopa compares to other available treatments for patients with symptomatic NOH.
- Overall, there is low quality of evidence for the use of droxidopa in patients with symptomatic NOH (Refer to Appendix A).

Study 301³

- Study 301 was a Phase 3 multicenter, multinational, double-blind trial that randomized 162 patients (i.e., 61.6% of 263 patients who were considered responders (i.e., ≥ 1 unit on the OHQ item 1 ["dizziness, lightheadedness, feeling faint, and feeling like you might black out"], in addition to ≥ 10 mm Hg increase in SBP from baseline) after an open-label droxidopa optimization protocol) with symptomatic NOH due to Parkinson's disease (N=66), multiple symptom atrophy (N=26), pure autonomic failure (N=54), or nondiabetic autonomic neuropathy (N=8), with a decrease in systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within 3 minutes after standing, to treatment with droxidopa or placebo.³
- 97% Caucasian, 52% male, with a mean age of 56³; 45% of participants were taking dopa-decarboxylase inhibitors, and 29% were taking fludrocortisone¹
- The Orthostatic Hypotension Questionnaire (OHQ) consists of 10 items, 6 which address NOH symptoms (e.g., dizziness/lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, head/neck discomfort), and 4 that ask the patient to consider the impact of NOH on daily activities in the preceding week (e.g., that require "standing a short time," "standing a long time," "walking a short time," and "walking a long time"). A Likert scale is used to score the item from 0 (not bothered/no interference) to 10 (worst possible/complete interference). A composite symptom score and a composite symptom-impact score (each an average of the item scores that are not rated 0 at baseline), as well as an overall composite score (average of the symptom and symptom-impact composite scores), are computed based on patient response.³

- The primary efficacy endpoint was change in overall composite score from randomization to end of study (at Week 1 analysis). Secondary endpoints included: change in symptom score; change in symptom-impact composite score; and change in individual OHQ items. Additional endpoints included change in standing systolic BP from randomization to end of the study.³
- Patients with symptomatic NOH (who previously responded to open-label droxidopa) treated with droxidopa for one week experienced a statistically significant improvement in OHQ composite score, composite symptom score, composite symptom-impact score, and increase in standing systolic BP compared to placebo. There was a statistically significant improvement noted in four of the six components of the symptom score (dizziness/lightheadedness, vision disturbance, weakness, fatigue), as well as all four of the symptom-impact items (standing short time, standing long time, walking short time, walking long time).
- Post-hoc subgroup analyses showed statistically significant differences favoring droxidopa in OHQ composite score as well as standing systolic BP only for patients with pure autonomic failure, or for non-users of dopa-decarboxylase inhibitors. It was noted that it is difficult to assess efficacy by subgroup as each contained fewer than 50 patients.³

Study 301 Results³

Endpoint	Droxidopa (N=82)	Placebo (N=80)	Difference (95% CI)	P
	Mean (SD) change from randomization			
OHQ Composite score	-1.83 (2.07)	-0.93 (1.69)	0.90 (0.30-1.48)	0.003
OHQ Composite symptom score	-1.68 (2.13)	-0.95 (1.90)	0.73 (0.10-1.36)	0.010
OHQ Composite symptom-impact score	-1.98 (2.31)	-0.92 (1.82)	1.06 (0.41-1.71)	0.003
Standing SBP (mm Hg)	11.2 (22.9)	3.9 (16.3)	7.3 (1.1-13.5)	<0.001

CI=confidence interval; OHQ=Orthostatic Hypotension Questionnaire; SBP=systolic blood pressure; SD=standard deviation

Study 306B¹

- Study 306B (unpublished data) was a Phase 3 multicenter, double-blind, randomized trial in 171 patients (147 included in efficacy analysis) with symptomatic NOH and Parkinson's disease, with a decrease in systolic BP \geq 20 mmHg or diastolic BP \geq 10 mmHg within 3 minutes after standing, who were treated with droxidopa (100 mg to 600 mg three times daily) or placebo for 8 weeks after a 2 week titration period.¹
- Per the product information, most of the patients were Caucasian, with a mean age of 72 years; 88% of participants receiving droxidopa and 94% of those on placebo were taking dopa-decarboxylase inhibitors; 26% on droxidopa and 17% on placebo were taking fludrocortisone.¹
- At Week 1, there was a statistically significant decrease of 0.9 units (from a mean baseline of 5.1) in the OHQ item for dizziness with droxidopa compared to placebo (P=0.028); although, this effect did not continue beyond Week 1.¹
- At Week 1, patients treated with droxidopa had a statistically significantly greater increase in the lowest standing systolic BP (5.6 mmHg; P=0.032).¹
- In addition to results from Study 306B, the product information states that the treatment benefit of droxidopa beyond 2 weeks is unknown, based on results from Study 303 (extension of Study 301 and 302, which was a 2 week withdrawal study) where patients received droxidopa for three months, then a 2 week withdrawal phase, that did not find a significant benefit between treatment and placebo.¹ In addition, results from study 301 and Study 306B that analyzed treatment effect at Week 1, were in patients who received prior therapy with droxidopa during the 1 to 2 week titration period.²
- Study 306A (originally Study 306), conducted in 51 patients with Parkinson's Disease and symptomatic NOH, found no statistically significant difference in the primary endpoint of mean change in composite OHQ score from baseline to Week 8 with droxidopa (-2.2) compared to placebo (-2.1), and was therefore stopped and considered exploratory. The authors noted a numerically greater improvement in the secondary endpoint of OHQ item 1 (dizziness/lightheadedness) score with droxidopa compared to placebo (P=0.24), that was greater at Week 1 compared to subsequent evaluations (Weeks 2, 4, 8). A similar number of patients reported falls in the droxidopa group (54%) compared to placebo (59%); with the authors reporting the average number of falls per patient on droxidopa as 0.4, compared to 0.8 on placebo (RR 0.5; P=0.16).¹¹

Potential Off-Label Use

- Droxidopa is marketed in Japan for: 1) improvement of frozen gait and dizziness on standing in Parkinson's disease (Yahr stage III); 2) improvement of orthostatic hypotension, syncope, and dizziness on standing in Shy-Drager syndrome [a.k.a. Multiple System Atrophy, that has FDA approval] and familial amyloid polyneuropathy; and 3) improvement of orthostatic hypotension symptoms in the hemodialytic patient (dizziness, lightheaded feeling, dizziness on standing up, malaise, and weakness).⁴
- Droxidopa has been used in the management of orthostatic hypotension in spinal cord injury patients, with preliminary results from one small, open-label dose titration study in VA patients showing an increase in seated SBP (e.g., statistically significant difference with 400 mg three times daily vs. placebo, 100 mg or 200 mg three times daily at 1 and 2 hours post dose; significant vs. placebo and 100 mg three times daily at 3 hours post dose), per post hoc analysis.¹⁴

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning¹	<ul style="list-style-type: none"> • WARNING: SUPINE HYPERTENSION Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue droxidopa [see <i>Warnings and Precautions</i>]
Contraindications¹	<ul style="list-style-type: none"> • None
Warnings/Precautions¹	<ul style="list-style-type: none"> • Supine Hypertension Droxidopa may cause or exacerbate supine hypertension in patients with NOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Blood pressure should be monitored both in the supine position when in the head-elevated sleeping position. If supine hypertension persists, droxidopa should be discontinued or the dose reduced as supine hypertension may increase the risk of cardiovascular events. • Hyperpyrexia and Confusion Case reports of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with droxidopa during post-marketing surveillance. Patients should be observed carefully if the dose of droxidopa is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. Although NMS is uncommon, it can be life-threatening where early diagnosis is important to ensure appropriate treatment. NMS is characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. • Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure Droxidopa may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Consider risk vs. benefit prior to initiating therapy in patients with these conditions. • Allergic Reactions Droxidopa contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions, including bronchial asthma, in certain susceptible persons (e.g., patients with aspirin hypersensitivity).

Safety Considerations^{1,3}

- In Study 301, during double-blind treatment, no falls occurred in the droxidopa treatment group compared to 3.7% of patients on placebo. Cardiac adverse events were reported in 3.0% of patients during the open-label dose titration phase of droxidopa, most frequently reported as palpitations (1.9%). During the treatment phase, no cardiac adverse events and no serious adverse events were reported. At the end of the study, 4 patients (4.9%) receiving droxidopa experienced supine hypertension (defined as systolic BP > 180 mm Hg), which was reported in 2 patients (2.5%) in the placebo group.³
- According to data from long-term, open-label extension trials (N=422), the most common adverse events reported were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).¹

Adverse Reactions^{1,2}

Common adverse reactions ¹ (Study 301, 302, 306)	Headache (6.1-13.2%), dizziness (3.8-9.6%), nausea (1.5-8.8%), and hypertension (1.5-7.0%) were noted more frequently with droxidopa compared to placebo
Death/Serious adverse reactions ^{1,2}	Supine hypertension; hyperpyrexia and confusion (refer to Warnings/Precautions) ¹ Per FDA review, a total of 27 deaths occurred in the clinical trials submitted for FDA approval, with 16 deaths reported in the original application, 1 in the 90-day safety update, and 10 in the long-term uncontrolled study 304. There were no deaths in study 306, submitted for subsequent review.
Discontinuations due to adverse reactions ¹	Most common included hypertension or increased blood pressure, nausea

Drug Interactions¹**Drug-Drug Interactions¹**

- Concomitant use of a dopa-decarboxylase inhibitor (e.g., carbidopa) may require dosage adjustments of droxidopa. Patients receiving droxidopa in addition to levodopa/dopa-decarboxylase inhibitor combination experienced a decrease in the clearance of droxidopa with subsequent increased exposure of 100%; however, no dosage adjustments were needed or increase in associated adverse events noted in clinical trials when used in combination.
- Concomitant administration of droxidopa with other medications that increase blood pressure may increase the risk for supine hypertension (refer to product information).

Drug-Food Interactions¹

- Administration of droxidopa with a high fat meal resulted in a moderate decrease in exposure of the drug, with a delay in absorption by approximately 2 hours.

Risk Evaluation

As of October 30, 2014

115 of October 30, 2017

Comments																
Sentinel event advisories	<ul style="list-style-type: none">None															
Look-alike/sound-alike error potentials	<table><tr><th>NME Drug Name</th><th>Lexi-Comp</th><th>First DataBank</th><th>ISMP</th><th>Clinical Judgment</th></tr><tr><td>Droxidopa 100mg, 200mg, 300mg cap</td><td>Levodopa Carbidopa Droxia</td><td>None</td><td>None</td><td>Methyldopa</td></tr><tr><td>NORTHERA</td><td>None</td><td>None</td><td>None</td><td>Norethindrone</td></tr></table> <ul style="list-style-type: none">Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment	Droxidopa 100mg, 200mg, 300mg cap	Levodopa Carbidopa Droxia	None	None	Methyldopa	NORTHERA	None	None	None	Norethindrone
NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment												
Droxidopa 100mg, 200mg, 300mg cap	Levodopa Carbidopa Droxia	None	None	Methyldopa												
NORTHERA	None	None	None	Norethindrone												

Other Considerations

According to the FDA medical review, the original application for approval of droxidopa included data from three studies with an enriched population (e.g., that enrolled responders), where only one study (Study 301) met the primary endpoint. It was also noted that this study included one site that contributed a disproportionate number of patients with highly positive results.² Resubmission included data from an additional trial (Study 306B), that was an amendment from the original trial (Study 306) that had met criteria for futility after an unblinded interim analysis of the primary endpoint of change in OHQ from baseline to Week 8 (becoming Study 306A). The primary endpoint for Study 306B was then amended to patient-reported falls, and later modified to OHSA item-1 from baseline to Week 1.² Study 306B was also noted to have an imbalance of premature discontinuations, resulting in 78% of patients on droxidopa and 92% of patients in the placebo group included in the efficacy analysis set.²

Droxidopa (NORTHERA) is only available through specialty pharmacies:

- CVS/Caremark has been selected by the manufacturer as the exclusive specialty pharmacy to dispense droxidopa to VA patients.
- The prescriber should complete and forward the VA specific NORTHERA Treatment Form to the VA Pharmacy for review.
- After review, the VA Pharmacy will fax the form to CVS/Caremark Specialty Pharmacy for the prescription to be filled. CVS/Caremark Specialty Pharmacy will send the dispensed prescription directly to the patient or to the VA Pharmacy for relay to the patient as indicated on the NORTHERA Treatment Form. The specialty pharmacy will also fax a delivery confirmation summary to the ordering pharmacy within 72 hours for any prescription shipped directly to a patient.
- The VA Pharmacy should include the purchase order number on the VA specific NORTHERA Treatment Form for the first time the prescription is dispensed to the patient; CVS/Caremark will contact the VA Pharmacy for a dispensing and payment authorization before each refill is shipped.
- CVS/Caremark Specialty Pharmacy does not require a pharmacy account application. The NORTHERA Treatment Form (found on the NORTHERA Web site) available to the private sector should not be used. It also contains program information and details that do not apply to the VA.
- The ordering summary along with the NORTHERA Treatment Form for VA Patients are posted on PBM's SharePoint site:
<https://vaww.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/Forms/AllItems.aspx>.

Dosing and Administration¹

- The recommended starting dose of droxidopa is 100 mg, taken orally three times daily: upon arising in the morning, at midday, and in the late afternoon at least 3 hours prior to bedtime (to reduce the potential for supine hypertension during sleep).
- Doses should be titrated to symptomatic response, in increments of 100 mg three times daily every 24 to 48 hours up to a maximum dose of 600 mg three times daily (i.e., a maximum total daily dose of 1,800 mg).
- Monitor supine blood pressure prior to initiating droxidopa and after dose increase.
- Droxidopa should be administered consistently, either with food or without food.
- Droxidopa capsules should be administered whole.
- Patients who miss a dose of droxidopa should take their next scheduled dose.

Special Populations (Adults)¹

	Comments
Elderly	<ul style="list-style-type: none"> • No overall differences in safety or effectiveness were noted in patients 75 years of age or older with symptomatic NOH included in the droxidopa clinical program; however, the manufacturer notes that greater sensitivity of some older patients cannot be ruled out.
Pregnancy	<ul style="list-style-type: none"> • Droxidopa is Pregnancy Category C • There are no adequate and well-controlled trials in pregnant women. • Increased incidence of lower body weight and undulant rib, that spontaneously reversed after birth were noted in fetuses of rats that received up to 3 times the maximum recommended total dose in humans. Shortening of the gestation period was also observed in rats at approximately 3 times the maximum recommended total dose in humans. Low incidences of renal lesions were observed in female rats treated with droxidopa.
Lactation	<ul style="list-style-type: none"> • Droxidopa is excreted in breast milk in rats, with reduced weight gain and reduced survival observed in the offspring.
Renal Impairment	<ul style="list-style-type: none"> • Patients with mild to moderate renal impairment (glomerular filtration rate [GFR] > 30 ml/min) were included in clinical trials and did not experience an increase in adverse reactions. There is limited experience with droxidopa in patients with GFR < 30 ml/min.
Hepatic Impairment	<ul style="list-style-type: none"> • No data identified.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified.

Projected Place in Therapy

- Orthostatic hypotension is defined as a decrease in systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within 3 minutes after standing. Orthostatic hypotension may or may not be accompanied by symptoms (e.g., dizziness, lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, head or neck ache).¹⁵ Orthostatic hypotension increases with age¹³ and is reported to affect approximately 30% of those over the age of 65.¹⁰
- Neurogenic orthostatic hypotension is a result of the inability of the autonomic nervous system to adequately release norepinephrine in order to regulate blood pressure after changes in posture, and can be seen in patients with Parkinson's disease, pure autonomic failure, and multiple system atrophy.⁴ Patients may experience a sustained decrease in blood pressure upon standing, as well as supine hypertension.⁴ It is reported that Parkinson's disease affects approximately one to 1.5 million Americans, with an estimate of 20%⁴ to 37-58%¹⁶ of patients with Parkinson's disease with symptomatic NOH. Multiple system atrophy is a rare disorder, but the prevalence rate of orthostatic hypotension in these patients is estimated to be 75%, and 100% in patients with pure autonomic failure, also a rare condition.¹⁶
- The management of symptomatic orthostatic hypotension should begin with identification of any underlying cause, including review of the patient's current medications to avoid or minimize agents that may contribute to hypotension (e.g., diuretics, antihypertensive agents, antianginal medications, alpha-adrenergic blockers, antidepressants, etc.).^{4,8,16}
- Non-pharmacologic measures should also be implemented, as indicated and tolerated:^{4,8,16}
 - Adequate salt and fluid intake
 - Physical maneuvers (e.g., toe-raises, crossing legs, squatting, bending at the waist)
 - Compression stockings or garments
 - Night time head-up tilt
 - Stepwise raising from supine to standing
- Pharmacologic management may include:
 - Fludrocortisone (available on the VA National Formulary), has been used to increase plasma volume, and therefore blood pressure.¹⁶ Fludrocortisone has been used off-label as monotherapy or in combination with other treatments for orthostatic hypotension.^{1,6,12,16}
 - Midodrine (an alpha1-adrenergic agonist) is FDA approved for symptomatic NOH^{5-8,13} and is available on the VA National Formulary. Data are limited and there are no comparison trials with midodrine and droxidopa to help determine place in therapy of these two agents.^{1-7,13}
 - Without comparison data, place in therapy of droxidopa should be determined on a case by case basis based on patient response and tolerability to alternate agents available on the VA National Formulary, convenience, and cost of treatment.
 - Droxidopa is FDA approved for adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy. Additional data are needed to determine the benefit of droxidopa for off-label use (e.g., symptomatic orthostatic hypotension in patients with diabetic autonomic neuropathy, spinal cord injury, on hemodialysis). There is the potential for decreased response to droxidopa in patients receiving concomitant treatment with a dopa-decarboxylase inhibitor (e.g., carbidopa) for the management of Parkinson's Disease; the clinical impact of this drug interaction has yet to be determined.
 - Product labeling for droxidopa includes a Boxed Warning for supine hypertension. It is recommended to monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue droxidopa as supine hypertension may increase the risk of cardiovascular events. In addition, as droxidopa is a prodrug metabolized to norepinephrine, it may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Consider risk vs. benefit prior to initiating therapy in patients with these conditions.
 - If droxidopa is initiated, it should be noted that only patient responders were enrolled in the published pivotal clinical trial of droxidopa (Study 301). Therefore, initial patient response and tolerability to droxidopa should be assessed (with discontinuation if there is no clinical benefit or intolerable adverse

- effects); with continued effectiveness of droxidopa reassessed periodically due to the benefit beyond 2 weeks of treatment not yet been established in clinical trials.
- Other treatments have also been used for orthostatic hypotension, most with limited data.^{10,14}
- Overall, there is low quality of evidence for the use of droxidopa in patients with symptomatic NOH (Refer to Appendix A as well as sections on Efficacy and Other Considerations).

References

1. NORTHERA (droxidopa) [prescribing information]. Deerfield, IL: Lundbeck. August 2014.
2. Droxidopa. Medical Review. Center for Drug Evaluation and Research. Drugs@FDA. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203202Orig1s000TOC.cfm. Accessed October 28, 2014.
3. Kaufmann H, Freeman R, Biaggioni I, et al., On behalf of the NOH301 Investigators. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. *Neurology* 2014;83:328-35.
4. Isaacson S, Skettini J. Neurogenic orthostatic hypotension in Parkinson's disease: evaluation, management, and emerging role of droxidopa. *Vasc Health Risk Manag* 2014;10:169-76.
5. Wright RA, Kaufmann HC, Perera R, et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology* 1998;51:120-4.
6. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. *JAMA* 1997;277:1046-51.
7. Jankovic J, Gilden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. *Am J Med* 1993;95:38-48.
8. Low PA, Wolfgang S. Update on management of neurogenic orthostatic hypotension. *Lancet Neurol* 2008;7:451-8.
9. Campbell IW, Ewing DJ, Clarke BF. 9-Alpha-fluorohydrocortisone in the treatment of postural hypotension in diabetic autonomic neuropathy. *Diabetes* 1975;24:381-4.
10. Logan IC, Witham MD. Efficacy of treatments for orthostatic hypotension: a systematic review. *Age and Ageing* 2012;41:587-94.
11. Hauser RA, Hewitt LA, Isaacson S. Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A). *J Parkinsons Dis* 2014;4:57-65.
12. NICE National Institute for Health and Care Excellence. Evidence summary: unlicensed or off-label medicine. Postural hypotension in adults: fludrocortisone. 01 October 2013. <http://www.nice.org.uk/advice/ESUOM20>
13. NICE National Institute for Health and Care Excellence. Evidence summary: unlicensed or off-label medicine. ESUOM5: Postural hypotension in adults: midodrine. 05 February 2013. <http://www.nice.org.uk/advice/ESUOM5>
14. Wecht JM, Rosado-Rivera D, Weir JP, Ivan A, Yen C, Bauman WA. Hemodynamic effects of L-threo-3,4-dihydroxyphenylserine (droxidopa) in hypotensive individuals with spinal cord injury. *Arch Phys Med Rehabil* 2013;94:2006-12.
15. Schatz IJ, Bannister R, Freeman RL, et al., for the Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996;46:1470.
16. Metzler M, Granata R, Robertson D. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. *J Neurol* 2013;260:2212-9.

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.